PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

DIQUAT

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Public Health Goal for
DIQUAT
In Drinking Water

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or

MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

TABLE OF CONTENTS

PUBLIC HEALTH GOAL FOR DIQUAT IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.015 mg/L (15 ppb) is developed for the pesticide diquat in drinking water. Several animal toxicity studies are relevant to defining the PHG level, including reports of minimal lens opacities and cataracts in rats and dogs, and developmental defects in rabbits and mice. Rats (50 CD rats/sex/dose) were administered diquat at concentrations of 0, 5, 15, 75, or 375 ppm in the feed for 104 weeks, and 10 more of each group for an interim sacrifice at 52 weeks (Colley et al., 1985). The approximate lifetime doses were estimated to be 0, 0.19, 0.58, 2.91, or 14.88 mg/kg-day for male rats, and 0, 0.24, 0.72, 3.64, or 19.44 mg/kg-day for female rats. A few cataracts were observed by 13 weeks at the highest doses, and in nearly all the rats fed 375 ppm diquat by 52 weeks. At two years, lens opacities were noted in both male and female rats at 15 ppm (1/22 and 1/20), at 75 ppm (3/21 and 3/20), and 375 ppm (24/24 and 27/27). Based on this study, an estimated no-adverse-effect-level (NOAEL) of 0.22 mg/kg-day (the average of male and female doses) for minimal lens opacities in a chronic dietary study in rats was chosen as the critical effect.

The PHG is calculated from this toxicity value using a 100-fold uncertainty factor to allow for intraspecies differences and potential sensitive human subpopulations. Studies of the carcinogenic potential of diquat are considered to be negative and therefore no health-protective concentration was calculated for diquat based on the cancer endpoint. The PHG should be low enough to protect against all adverse effects of diquat in drinking water, including any potential effects in infants and children. Diquat can persist in soils, but is so tightly bound that it is not bioavailable. It can be applied as an aquatic herbicide to certain surface waters, but is rarely found in drinking water supplies because of rapid uptake into sediments.

The existing U.S. Environmental Protection Agency (U.S. EPA) and California maximum contaminant level (MCL) is 0.02 mg/L (20 ppb).

INTRODUCTION

The purpose of this document is to describe the development of a PHG for the herbicide diquat in drinking water. In California, this chemical is primarily used as a desiccant on alfalfa (for animal fodder) and as a nonselective herbicide to control broadleaf weeds for landscape maintenance, rights of way, and plants in containers in nurseries. Diquat is used in smaller quantities as an aquatic herbicide, on clover used for forage, on potatoes, and on uncultivated agricultural areas (DPR, 1999a). It is applied in aqueous solution in the form of a dibromide salt; common trade names are Reglone, Dextrone, and Aquacide. Diquat was first registered for use in the United States in 1961.

Diquat is closely related to paraquat, another quaternary bipyridilium herbicide. Their properties and uses are similar, although about ten times more paraquat than diquat is applied annually in California. The greatest use of paraquat is as a desiccant on cotton; it also is applied as a desiccant to alfalfa, used to control weeds in orchards and vineyards, and used in minor quantities on many other crops. These compounds alter oxidation/reduction cycles and thus interfere with photosynthesis, resulting in rapid toxicity to foliage.

CHEMICAL PROFILE

Chemical Identity

Diquat, 1,1'-ethylene-2,2'-dipyridylium, is a charged quaternary ammonium compound used in commerce as the dibromide salt. The structure of diquat dibromide and that of the closely related herbicide paraquat are shown in Figure 1.

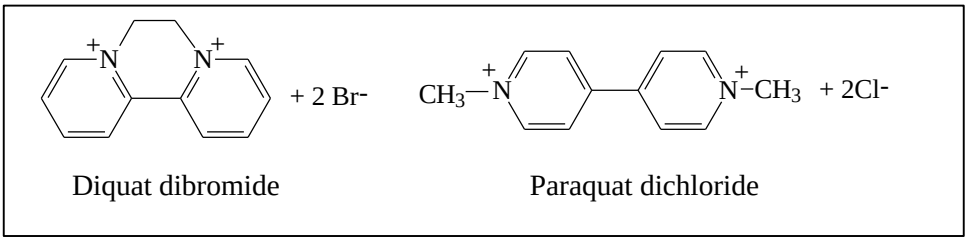

Figure 1. Chemical Structures of Diquat and Paraquat.

Chemical synthesis may result in the formation of a trace of ethylene dibromide, but this has been judged to be of no toxicological significance (U.S. EPA, 1995). The technical grade product is greater than 95 percent pure diquat dibromide; it is formulated in water at about 35 percent diquat cation, which is approximately two pounds diquat cation/gallon. All references to diquat amounts and concentrations in this document refer to the diquat cation. Because of the corrosive nature of concentrated aqueous solutions of diquat, the formulation contains corrosion inhibitors.

Physical and Chemical Properties

The physical and chemical properties of diquat are summarized in Table 1. The charged quaternary ammonium structure of diquat gives it high water solubility. The positive charges are also responsible for binding to anionic sites on soil or sediments. This is a different phenomenon than the binding of many pesticides, which adsorb to lipophilic binding sites on soil organic matter. Tight binding to soil or to particles suspended in the air or water column serves to protect diquat from degradation, limit its biological activity, and decrease its environmental mobility.

Production and Uses

The total usage of diquat dibromide in California in 1997 was 93,000 pounds (the most recent data), while use of paraquat dichloride totaled 911,000 pounds (DPR, 1999a). The Hazardous Substances Data Bank provides no information on recent production of diquat, but indicates that all diquat was imported in 1977 and 1982, comprising a total of 834,000 pounds (HSDB, 1998). California use of diquat has apparently stabilized after decreasing in recent years; total usage was 199,000 pounds in 1989, 162,000 pounds in 1990, 133,000 pounds in 1991, and 87,000 pounds in 1995 (DPR, 1994, 1995). The Department of Pesticide Regulation's (DPR's) current online database lists only one diquat product with an active registration, listed as "Diquat Herbicide, 10182-353-AA," (Zeneca) containing 36.4 percent diquat dibromide.

Diquat is supplied only as a liquid formulation, and all applications are further diluted in water for use. It is generally sprayed directly onto foliage to kill it or to dry it out before harvest (e.g., alfalfa). Application rates range from 0.25 to 4.0 pounds of active ingredient per acre. Diquat may be applied alone or in combination with other herbicides such as paraquat, amitrole, or simazine (DPR, 1994). Diquat is approved for use on a wide variety of human food crops as well as animal fodder, and can be used for weed control on farms, industrial sites, irrigation systems, lakes and ponds, golf courses, and uncultivated areas.

Table 1. Summary of diquat dibromide properties

Property	Values*
Molecular weight	344.05
Color	colorless to yellow crystals, reddish in solution
Physical state	formulated as aqueous solution
Odor	none (irritant)
Odor threshold	NA
Melting point	320 ^{o}C, 335-340 ^{o}C
Boiling point	decomposes
Solubility	
Water	ca. 700 g/L
Organic solvents	slightly soluble in alcohols, insoluble in nonpolar organics
Density	1.22-1.27 at 25 ^{o}C
Partition coefficients	
Log K_{ow}	-3.05, -4.60
Log K_{oc}	0.42
Vapor pressure	$<1x10^{-5}$ mm Hg at 20 ^{o}C
Henry's Law Constant	$<6.3x10^{-14}$ atm-m^3/mol at 20-25 ^{o}C

* HSDB, 1998; Merck Index, 1996; Montgomery, 1993.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

The very low volatility of diquat limits its potential concentration in air. In the atmosphere it will be present almost entirely as an aerosol, mainly from spray drift. The photolysis half-life has been estimated as two days under these conditions, although droplet settling is the predominant removal mechanism (HSDB, 1998). Diquat may also be redistributed into air, bound to fine soil or sediment particles. This is not likely to result in any biological effects because of the tight, virtually irreversible, binding to soil anionic sites.

Exposure to diquat in spray drift may result in a significant hazard to workers and to aquatic and terrestrial non-target organisms. This has been the subject of evaluation by the Spray Drift Task Force convened by U.S. EPA.

Soil

Diquat binds tightly to soil organic matter, which makes it immobile in the environment. In several field degradation studies, no detectable degradation occurred after intervals as long as three years. Its soil half-life could not be calculated (U.S. EPA, 1995). This may lead to accumulation of diquat in treated soils. Little or no diquat hydrolysis occurs at normal soil pHs. It is also very slowly photolyzed in soil, and is not measurably microbially degraded under either aerobic or anaerobic conditions (DPR, 1994; U.S. EPA, 1995). However, the duration of activity of diquat in soil tends to be limited by irreversible soil binding. Its tight binding to clay is considered to produce an effective means of immobilizing and inactivating the chemical in the case of spills (HSDB, 1998).

Water

Diquat removal from surface water is primarily due to binding to suspended sediment (Shaw and Hopke, 1975). The rate of loss is related to water turbidity and sediment settling rate. Under environmental conditions the effective half-life ranges from about two to ten days. Photolysis can also remove diquat from surface water; its photodegradation half-life in natural sunlight has been estimated from 14 to 74 days (Montgomery, 1993; DPR, 1994).

Diquat was not detected in water from California wells in the most recent sampling, according to the 1996 and 1997 Well Inventory Reports (DPR, 1999b).

Food

Tolerances exist for diquat on a number of food products, including vegetables, meat, milk, and eggs. Tolerances are set for diquat direct uses (application to fields for weed control or desiccation of foliage) under 40 CFR 185.226a, and for diquat applied to water for weed control, which may result in indirect residues in foods under 40 CFR 185.226b. The residues in meat, eggs, and milk could be the result of both direct and indirect uses, but are listed with direct uses (as cited in U.S. EPA, 1995).

Tolerances for direct application of diquat are 0.05 ppm for meat products, 0.02 ppm for milk, and 0.1 ppm for potatoes. Proposed tolerances are listed for alfalfa seed (3.0 ppm), grain sorghum (2.0 ppm), and soybeans for seed (0.2 ppm). Food tolerances for diquat residues derived indirectly (from application of diquat to ponds, lakes, reservoirs, marshes, etc.) vary between 0.02 ppm and 20 ppm. The values proposed under the 1995 reassessment are 0.02 ppm for cucurbits, fruits, grain crops, nuts, and root, seed, and pod vegetables; 0.05 ppm for fruiting and leafy vegetables; 0.1 ppm for avocado, cottonseed, grasses, hops, and sugarcane; 2.0 ppm for fish; and 20 ppm for shellfish. In addition, tolerances are listed under other subsections for residues which can increase during processing, including 1.0 ppm for processed potatoes as potato flakes and 0.5 ppm for potato chips under section 185.2500c; and 1.0 ppm for potato waste and 0.6 ppm for soybean hulls under 186.2500 (as cited in U.S. EPA, 1995).

Other Sources

No other diquat sources are identified or expected.

METABOLISM AND PHARMACOKINETICS

Absorption

Diquat crosses cell membranes mostly by diffusion, although some active transport may occur via cation pumps (Charles et al., 1978; Saito, 1986). Diffusion of chemicals across biological membranes is facilitated by ability to dissolve in both aqueous and lipid phases. Diquat, paraquat, and other highly charged cationic compounds cannot dissolve in a lipid phase, and therefore do not readily cross biological membranes (Czyzewska et al., 1984). Tight binding of diquat to anionic sites in various substrates (such as dermally contacted soil and some food components) also limits its availability for systemic uptake.

Gavage administration of 5 or 10 mg/kg ^{14}C-labelled diquat dibromide to male Wistar rats resulted in excretion of 4 to 6 percent in urine, and 90 to 97 percent in the feces (Daniel and Gage, 1966). In the same study, subcutaneous administration resulted in 88 to 98 percent urinary excretion of the radiolabel, versus about 2 percent excretion in the feces, indicating that biliary excretion is minimal. In another study, male rats were administered 45 mg/kg diquat dibromide by gavage (Mills, 1976). Six percent of the compound was recovered in urine in 96 hours, and 89 percent in feces. After subcutaneous injection, 87 percent was excreted in urine, and 5 percent in feces. The urinary constituent was identified as mostly unchanged diquat.

Oral administration of 7 mg/kg of ^{14}C-diquat to a single female goat resulted in excretion of 94.2 percent of the radioactivity in the feces, 2.2 percent in the urine, and 0.018 percent in the milk in seven days (Griggs and Davis, 1973). Oral dosing of four lactating cows with 5 mg/kg ^{14}C-diquat resulted in urinary excretion of less than 5 percent of the dose, and less than 0.02 percent in milk (Stevens and Walley, 1966). Even less ^{14}C-label was excreted in the urine (0.4 percent of the total) when the ^{14}C-diquat was absorbed onto barley straw first (Hemingway et al., 1974).

No information is available on oral absorption of diquat in humans. Absorption is likely to be highest from water, perhaps slightly lower from food, and insignificant from soil. For the calculation of the PHG, human oral absorption will be estimated as 10 percent from both food and water, and 0 percent from soil (if applicable).

Absorption of diquat from the lung appears to be very efficient (Charles et al., 1978), although it is not actively transported into lungs as is paraquat. The high toxicity of diquat administered as an aerosol (Bruce and Griffis, 1987) also indicates high availability, which should be assumed to be about 70 percent of the respirable fraction of inhaled aerosol particles. Exposure to diquat in the vapor phase can be assumed to be negligible.

Dermal absorption of diquat appears to be very low. The dermal LD_{50} of diquat in male Sherman rats is estimated as 433 mg/kg, compared to an oral LD_{50} of 147 mg/kg (Gaines and Linder, 1986). Similarly, the dermal LD_{50} in rabbit has been estimated as 400 mg/kg, compared to an oral LD_{50} of 100 mg/kg (FAO, 1971). Thus, the oral toxicity appears to be three to four times as great as the dermal toxicity. This should be a rough measure of bioavailability because absorption is slow by both routes and metabolism is minimal. Assuming oral absorption of about 5 percent in both species, dermal absorption would therefore probably be about 1 to 2 percent in

rats and rabbits. However, absorption can increase with exposure to high concentration formulations because the resulting skin irritation can increase penetration.

Application of ^{14}C-diquat to human forearm skin for 24 hours at a concentration of 4 μg/cm resulted in urinary excretion of only 0.3 percent of the radioactivity in 120 hours (Feldmann and Maibach, 1974). In another human study, Wester and Maibach (1985) measured 1.4 percent of the label in the urine after occlusion of the application site. Correcting for a urinary recovery of 61 percent after intravenous administration (Feldmann and Maibach, 1974) yields an apparent dermal absorption in humans of 1 to 2 percent (at low, non-irritating concentrations). For the purpose of deriving a PHG, dermal absorption of diquat will be assumed to be 1 percent from water and zero from soil or ambient air.

Distribution

Diquat is distributed throughout the body in the aqueous phase, as expected for a hydrophilic, quaternary ionic compound. Unlike paraquat, it does not appear to be highly concentrated in the lung (Litchfield et al., 1973; Kurisaki and Sato, 1979). The slow passage across membranes can result in an apparent sequestration in various tissues as systemic levels rise and fall (Powell et al., 1983). In one rat study, diquat concentration was observed to be highest in spleen and next highest in kidney after 13.5 days of feeding (Minakata et al., 1995). Diquat as well as paraquat can accumulate into neuromelanin-containing tissues in frogs. This effect may not be noticeable in white rats and mice because of the limited amounts of neuromelanin in these species (Lindquist et al., 1988). There is little or no hepato/biliary/intestinal cycling of metabolites, but intact diquat is excreted into bile to some extent in humans (Ameno et al., 1994).

Metabolism

Diquat is minimally metabolized in all mammalian species tested. The metabolism that does occur is predominantly in the liver, apparently mediated by microsomal cytochrome P450 enzymes. Diquat increases the expression of several phase I and phase II enzymes in rat liver (Gallagher et al., 1995). In rat liver homogenates, diquat can be rapidly metabolized to monopyridone and dipyridone metabolites (Fuke et al., 1993); the lower metabolic rate in vivo may be due to slow uptake into hepatocytes. Humans also metabolize diquat to monopyridone and dipyridone forms (Fuke et al., 1996). Small amounts of a monopyridone metabolite and a 1,2,3,4-tetrahydro-1-oxopyrido (1,2a)-5-pyrazinium salt have been found in goat milk (Griggs and Davis, 1973).

Diquat also appears to support oxidation/reduction cycling involving a free-radical mechanism which generates superoxide and may lead to lipid peroxidation and cytotoxicity (Sandy et al., 1987; Rikans et al., 1993; Awad et al., 1994). This can occur in lung, liver, kidney, and cornea, resulting in the specific toxicity to these organs which is characteristic of the bipyridyl herbicides. The more potent effect of paraquat to increase O_2 consumption in lung, compared to diquat, may be part of the reason for the greater pulmonary toxicity of paraquat (Adam et al., 1990a,b) (although greater lung uptake of paraquat is probably the major reason). Formation of bipyridylium radicals by a reaction with oxygen in hepatocytes is not affected by inhibition of cytochrome P450 by carbon monoxide or metapyrone, suggesting an independent mechanism for this effect (DeGray et al., 1991). However, the mechanisms of the oxidative damage to proteins and the cytotoxicity are still unclear (Rikans and Cai, 1993; Blakeman et al., 1998).

Excretion

At least 90 percent of absorbed diquat is excreted in the urine. This is mostly in the form of the intact diquat ion, but the monopyridone and dipyridone metabolites have been identified in human urine (Fuke et al., 1996). Very small amounts of diquat may be found in milk, comprising less than 0.02 percent of the administered oral dose in cows (Stevens and Walley, 1966) and a goat (Griggs and Davis, 1973). Fecal excretion of the unabsorbed chemical accounts for more than 90 percent of an oral dose. Fecal diquat is predominantly the intact chemical moiety.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Oral administration of diquat can cause hepatic necrosis and oxidative damage (Smith et al., 1985; Smith, 1987; Tsokos-Kuhn et al., 1988; Spalding et al., 1989; Rikans et al., 1993; Awad et al., 1994; Vulimiri et al., 1995). A rat strain-specific component of this effect has been noted, in which Fischer rats suffer more hepatotoxicity than Sprague-Dawley rats at diquat doses providing similar hepatic oxidant stress (Smith et al., 1985). Diquat also alters intestinal transport and increases intestinal secretions (Czyzewska, 1985; Rawlings et al., 1992, 1994; Anton et al., 1998), which can cause intestinal distension and diarrhea. However, diquat causes minimal lung lesions, compared to paraquat (Kurisaki and Sato, 1979; Lam et al., 1980). Systemic administration of high doses produces lethargy, weakness, and incoordination. Among mammals, estimated oral LD_{50} is least in the cow, at 30 mg/kg; and greatest in the rat, at about 220 mg/kg (DPR, 1994). Results in mouse, rabbit, guinea pig, and dog were intermediate, at 125, 100, 100, and 100 to 200 mg/kg, respectively (DPR, 1994). The oral LD_{50} in hens was estimated to be 200 to 400 mg/kg (Clark and Hurst, 1970). Acute 96-hr LC_{50}s for freshwater fish are listed as 21 ppm for rainbow trout, 14 ppm for fathead minnow, 7.8 ppm for largemouth bass, and 2.1 ppm for walleye pike, with 48-hr LC_{50}s of 11.2 ppm for rainbow trout and 16 ppm for northern pike (HSDB, 1998; Montgomery, 1993). The fish toxicity levels are considered to represent slight to moderate toxicity (U.S. EPA, 1995).

U.S. EPA estimated the diquat dermal LD_{50}, applied in water, to be 433 mg/kg (95 percent confidence limits 344 to 568) in male Sherman rat (Gaines and Linder, 1986). In rabbits, the dermal LD_{50} is also listed as 400 mg/kg (as the diquat ion) by DPR (1994), as 262 to 315 mg/kg (as the dibromide), or as 140 to 169 mg/kg (as the diquat ion) by U.S. EPA (1995). The concentrated or dilute herbicidal preparations also caused skin and eye irritation in the animal toxicity tests. Diquat was not a dermal sensitizer to guinea pigs (DPR, 1994).

The inhalation LD_{50} was reported as 0.97 mg/L in rats by DPR (1994, citing Bruce, 1985) and U.S. EPA (1995, citing Access #26385). Experimental parameters (exposure duration, particle size, effective dose) are not provided by either source.

Subchronic Toxicity

Dietary administration of diquat at 6.1 to 37.7 mg/kg to Sprague-Dawley rats for four weeks resulted in increased liver weight without liver histopathological changes (Colley et al., 1981). The no-observed-effect-level (NOEL) for increased liver weight was 6.1 mg/kg-day in males and 31.4 mg/kg-day in females. In SPF mice, gavage administration of diquat at 10 mg/kg-day and above for ten days resulted in severe signs, including hunched posture, dyspnea, ptosis, piloerection, and death (Palmer et al., 1977). Food consumption was markedly reduced, and animals suffered severe weight loss. At 5 mg/kg-day or less, effects on feed consumption and body weight were sporadic; piloerection was the only consistent sign at the 5 mg/kg-day dose, with a NOAEL of 2.5 mg/kg-day.

Repeated dermal application of diquat formulation (20.64 percent in water) to Sprague-Dawley rats produced dose-related dermal irritation leading to progressive skin lesions at doses of 5 to 80 mg/kg-day, expressed as the cation (Auletta, 1987). Erythema occurred at day two in rats at 20 mg/kg-day or more, but not until day eight in rats dosed at 5 mg/kg-day. Severe toxic effects including mortality (1/12, 5/12, 11/12) occurred at the higher doses (20, 40, or 80 mg/kg, respectively). The subchronic lowest-observed-adverse-effect-level (LOAEL) under these conditions was 5 mg/kg-day, with no experimental NOAEL. It should be noted that this is not a systemic effect, and therefore it should not be treated as a systemic dose.

Rabbits were treated dermally with diquat dichloride (concentration not stated) at 3.1 to 25 mg/kg-day for up to 20 days (Swan, 1963). Dose-related skin ulcerations apparently developed at all doses (DPR, 1994). Mortality was 1/10, 2/10, 9/10, and 10/10 at 3.1, 6.3, 12.5, and 25 mg/kg-day, respectively. Post-mortem examinations found ulceration of gastric mucosa, degeneration of renal convoluted tubules, hemorrhages in the thymus, and lung congestion. No NOAEL for skin lesions was noted; the LOAEL was apparently 3.1 mg/kg-day (for the local effect).

Subchronic inhalation exposures of Sprague-Dawley rats (10/sex/group, six hrs/day, five days/week for three weeks) were conducted to aerosolized diquat at 0.1 μg/L in air. The material applied was a liquid formulation diluted to 5 percent diquat cation in distilled water (Bruce and Griffis, 1987). Reticulocyte counts were significantly depressed in both males (44 percent) and females (56 percent). Blood platelet counts were also significantly depressed (16 percent) in males. This appears to be the study described by U.S. EPA (1995) as MRID 40640801, in which the same exposure concentration is called a "NOEL." U.S. EPA also describes a companion study (MRID 40301701) with higher diquat concentrations (0.49, 1.1, and 3.8 μg/L) and the same exposure conditions, in which there were treatment-related effects at all concentrations. Effects at 0.49 μg/L included increased lung weight in the males and lung lesions in both males and females. In a satellite group of males and females at the highest dose, allowed to recover for 21 days, all toxic effects except mottling and reddening of the lungs were reversed. Assuming the rats breathed 0.25 m^3 of air/day and weighed 200 g, the effective daily dose at the 0.1 μg/L level is 0.02 mg/kg-day. This level will be considered the subchronic inhalation LOAEL.

Genetic Toxicity

Diquat did not cause reverse mutation in Ames assays, with or without metabolic activation (DPR, 1994). However, it did cause forward mutations (Bignami and Crebelli, 1979). Diquat increased thymidine kinase two to three-fold for a positive result in the mouse lymphoma cell plate assay with L51784 cells (DPR, 1994; U.S. EPA, 1995). A decrease in the mitotic index and an increase in chromosomal aberrations was observed in human lymphocyte (in vitro) tests

(Richardson et al., 1986; Wildgoose et al., 1986). Lethal recessive mutations were induced in *Aspergillus nidulans* at 10 mg/mL. Many of the positive results were observed at relatively high concentrations (over approximately100 μg/mL), associated with cytotoxicity.

Diquat was not clastogenic in the mouse micronucleus test at 62.5 or 100 mg/kg (McGregor, 1974), and did not cause dominant lethal effects in mice at 0.1, 1 or 10 mg/kg for five days (Sheldon et al., 1986). In a rat study using in vivo diquat treatment (0, 225, 450, or 900 mg/kg by gavage) plus evaluation of in vitro thymidine incorporation, no unscheduled DNA synthesis in hepatocytes was observed at the two time points tested (4 and 12 hours) (Trueman, 1986). However, some hepatocyte toxicity was observed (U.S. EPA, 1995). Unscheduled DNA synthesis was observed in in vitro tests with human fibroblasts at 1 to 1,000 μM (Ahmed et al., 1977), and with "epithelial-like human embryo cells" over a concentration range of 20 to 2,000 μg/mL (Benigni et al., 1979).

Taken together, these studies indicate that genotoxic effects can occur with diquat, but may be limited by cytotoxicity and maximum tolerable dose. In addition, the poor membrane transport of diquat may restrict its access to the genome.

Developmental and Reproductive Toxicity

In a rat multigeneration reproductive study (Hodge, 1990), diquat dibromide was fed to 30 Wistar rats/sex/dose in the diet at concentrations of 0, 16, 80, or 400 ppm for 12 weeks (F_0 generation) before mating, and continued through weaning of their offspring (about 18 to 20 weeks, total). For the next generation (F_1), the maximum dietary concentration was reduced to 240 ppm at nine weeks because of adverse effects. Cataracts, keratitis, conjunctivitis, and iridocyclitis were observed in adult male and female rats at 240 and 400 ppm. Cataracts were not observed in F_1 pups. At ≥ 240 ppm there were body weight decreases, decreased food consumption, and adverse effects on the kidney in adults of both sexes, both generations. There was also tongue ulceration in both sexes in generation F_0 and females of F_1, and hard palate ulceration in both sexes in generation F_1. Pup body weight gain was reduced in both sexes for F_1 and F_2 generations at the highest dose, and for the male rats at 80 ppm and above. No adverse effects were noted on reproduction. In pups sacrificed at weaning, kidney weights of F_1 pups were reduced at the highest dosage, while kidney hydronephrosis was noted at this dose in both generations. The parental systemic NOAEL was 80 ppm, while the pup systemic NOAEL was 16 ppm. Corresponding dose levels would be 4 mg/kg-day for the 80 ppm adults at the consumption level of 0.05 mg/kg per ppm in the diet, and 1.6 mg/kg-day for the 16 ppm pups at an estimated consumption level of 0.1 mg/kg per ppm in the diet.

In another rat study (Fletcher et al., 1972), diquat dibromide was fed to 12 Wistar male and 24 female rats per dose at concentrations of 0, 125, or 500 ppm for three generations. Decreased body weight gain and cataracts were observed at 500 ppm in the parental generations. A previous smaller study in Wistar rats with the same doses and conditions (Griffiths et al., 1966) also showed decreased weight gain and cataracts at 500 ppm. From these studies, a NOAEL of 125 ppm, or 6.25 mg/kg-day was identified using the assumed feed consumption level of 0.05 mg/kg per ppm in the diet.

Diquat dibromide (26.2 percent diquat ion) was also administered by gavage to 24 female Wistar rats at 0, 4, 12, or 40 mg/kg-day on gestation days 7 through 16 (Wickramaratne, 1989). Feed consumption and weight gain were reduced by 36 and 22 percent, respectively, at 40 mg/kg-day. These measures were also slightly reduced at 12 mg/kg-day (8 and 11 percent, respectively), resulting in a NOAEL of 4 mg/kg. The offspring exhibited decreased weight gain, delayed

skeletal ossification, and hemorrhagic kidneys at 40 mg/kg. Therefore, the NOAEL identified from this study is 12 mg/kg-day.

In a developmental study, 20 New Zealand white rabbits per dose level were administered diquat dibromide (26.2 percent) at 0, 1, 3, or 10 mg/kg by gavage on gestation days 7 through 19. Animals were sacrificed on day 30 (Hodge, 1989). At the highest dose there was a significant increase in maternal mortality, an 80 percent decrement in body weight gain, stomach ulceration, liver histopathological changes, and intestinal vascular leakage. As judged by DPR (1994), there were delays in fetal ossification (ventral tubercle of the cervical vertebrae) at all doses and a small but significant increase in malformations at 1 and 10 mg/kg, but not at 3 mg/kg. The DPR interpretation of the fetal results is shown in Table 2. The fetal abnormalities were judged by DPR to result from delayed cell migration (DPR, 1994). It also judged the maternal "NOEL" to be 3 mg/kg-day.

Table 2. Developmental effects of diquat in rabbits

Parameter	Diquat dose (mg/kg-day)			
	0	**1**	**3**	**10**
Implants, N	173	157	153	116
Live fetuses, N	147	134	129	96
Delayed ossification, N (%)	1 (0.7)	6* (4.5)	6* (4.6)	10* (10.4)
Malformed fetuses, N (%)	2 (1.4)	8* (6.0)	4 (3.1)	7* (7.3)
Litters with malformations	2	8	4	5
Major malformations	1 craniofacial, 1 liver	4 craniofacial, 3 cardiac, 2 crooked joint; 1 urogenital	1 craniofacial, 1 cardiac, 2 gall bladder	2 craniofacial, 3 gall bladder, 1 diaphragm, 1 fused ribs

* $p < 0.05$ by Fisher's Exact Test

The same study was evaluated by U.S. EPA (1995) (identified as MRID 41198901). U.S. EPA's interpretation differs considerably from that of DPR. According to U.S. EPA, "nothing remarkable was observed in the low-dose (1 mg/kg/day) group." The mid-dose group exhibited a decrease in maternal weight gain and food consumption, significant only during the first three days of dosing. The high-dose group showed more severe effects on both of these parameters, which were sustained throughout the dosing period. Developmental effects were observed only in the high-dose (10 mg/kg-day) group. Liver histopathological abnormalities and disrupted skeletal ossification (ventral tubercle of the cervical vertebrae and partly ossified or unossified sixth sternebrae) were listed, but otherwise no increases in major malformations were identified. U.S. EPA identified the maternal "LOEL" and "NOEL" to be 3 mg/kg-day and 1 mg/kg-day, respectively, and the developmental LOEL and NOEL to be 10 mg/kg-day and 3 mg/kg-day, respectively. Considering both the evaluation of DPR and that of U.S. EPA, we concluded that the Hodge (1989) results provide a weak indication of developmental effects at 1 mg/kg-day, which should be considered in setting health-protective levels for diquat in drinking water.

In another developmental study in rabbits, 15 to 20 dams per group were administered diquat dibromide by gavage at doses of 0, 1.25, 2.5, and 5 mg/kg on gestation days 1 through 28, with sacrifice occurring on day 29 (Palmer and Pratt, 1974; identified by U.S. EPA as

MRID 00061635). The reporting of experimental details was poor in this document. The only maternal effect noted was a decrease in weight gain at 5 mg/kg-day. Early resorptions appeared to be increased, but no adverse developmental effects were reported. The maternal NOAEL was 2.5 mg/kg-day based on the decreased weight gain at 5 mg/kg-day, while the developmental NOAEL was 5 mg/kg-day (highest dose tested). Both DPR and U.S. EPA considered this to be an inadequate study because of analysis and reporting deficiencies.

Mice were also evaluated for developmental effects. Diquat was administered by gavage to groups of 32 to 34 female albino Alderley Park strain SPF mice at 0, 1, 2, or 4 mg/kg on gestation days 6 through 15, with sacrifice on day 17 (Palmer et al., 1978; MRID 00061637). The dams exhibited adverse clinical signs at the mid and high doses including piloerection, dyspnea, respiratory noise, and hunched posture. Decreased body weight gain occurred at the mid (-23 percent) and high (-29 percent) doses. There were also excess maternal deaths at these doses (3/33 and 5/34, respectively, not associated with gavage errors, according to U.S. EPA; 4/33 and 8/34, respectively, according to DPR). DPR (1994) noted adverse developmental effects (skeletal anomalies, exencephaly, premature opening of the eyes, and umbilical hernia) at 2 and 4 mg/kg-day. U.S. EPA (1995) reported decreased fetal body weight (-12 percent) and increased skeletal alterations at the highest dose (16/23 affected litters versus 9/27 affected litters in the controls). The maternal LOAEL and NOAEL appear to be 2 mg/kg-day and 1 mg/kg-day, respectively, while the developmental LOAEL and NOAEL appear to be 2 mg/kg-day and 1 mg/kg-day, respectively (associated with maternal toxicity).

Immunotoxicity

No studies were found on immunotoxic effects of either diquat or paraquat. Incidental observations of adverse effects on lymphoid tissues (Hodge, 1991) or thymus (Swan, 1963) are insufficient to support any conclusion on immunotoxic potential of diquat.

Neurotoxicity

Acute and subchronic neurotoxicity studies have been conducted in rats and evaluated by DPR (1994) and U.S. EPA (1995) for pesticide registration. In the acute study to assess delayed neuropathy, a single dose of diquat dibromide was administered by gavage to 10 Alpk:APfSD rats per sex/dose at 0, 25, 75, or 150 mg/kg (Horner, 1992a; MRID 42666801). Rats were assessed in a functional observational battery (FOB), including motor activity, after six hours and on days 8 and 15. Basic clinical observations were performed daily. No effects were observed in the FOB. At the highest dose, females had piloerection, diarrhea, urinary incontinence, nose and mouth staining, and abnormal gait and posture. One of these animals administered 150 mg/kg was sacrificed *in extremis* on day six. In the females dosed at 75 mg/kg, only the diarrhea and nose staining were observed. Little or no effects were observed in the males. There was no histological evidence of neurotoxicity in either sex, and the constellation of effects is not an indication of direct neurotoxicity. The NOAEL for clinical signs was 25 mg/kg.

In the subchronic study, 12 Alpk:APfSD rats/sex/dose were fed 0, 20, 200, or 400 ppm diquat dibromide (expressed as the cation) in the diet for up to 14 weeks (Horner, 1992b; MRID 42616101). The doses were estimated as 0, 1.6, 8.0, and 32.4 mg/kg-day for males and 0, 1.9, 9.5, and 38.5 mg/kg-day for females (U.S. EPA, 1995). FOB and motor activity were assessed; no effects were observed. Decreases in body weight and body weight gain, and cataracts were observed in both males and females at the highest dose. No histopathological effects were observed in the five rats/sex/dose which were examined at the end of the study. The study is

considered to be negative for neurotoxic effects. The NOAEL for cataracts and adverse effects on body weight gain was 8.0 mg/kg-day for males and 9.5 mg/kg-day for females.

Chronic Toxicity

Diquat dibromide was fed to 50 CD rats/sex/dose at 0, 5, 15, 75, or 375 ppm for 104 weeks, and 10 more of each group for an interim sacrifice at 52 weeks (Colley et al., 1985; MRID 00145855). The approximate lifetime doses were estimated by U.S. EPA to be 0, 0.19, 0.58, 2.91, or
14.88 mg/kg-day for male rats, and 0, 0.24, 0.72, 3.64, or 19.44 mg/kg-day for female rats. A few cataracts were observed by 13 weeks at the highest doses, and in nearly all of the rats fed 375 ppm diquat by 52 weeks. At two years, lens opacities were noted in both male and female rats at 15 ppm (1/22 and 1/20), at 75 ppm (3/21 and 3/20), and 375 ppm (24/24 and 27/27). Poor survival to two years for all groups limits the statistical power at this time point. However, lens opacities and cataracts were also noted in a high proportion of animals that died or were sacrificed because of a moribund state between 52 and 104 weeks. Both male and female rats also had decreased renal clearance and urine concentrating ability at the two highest doses. Tumor results are discussed in the following section.

The two-year NOAEL for cataracts was identified by DPR (1994) to be 5 ppm (or 0.22 mg/kg-day, a combined average dose for male and female rats) and by U.S. EPA (1995) to be 15 ppm (0.58 mg/kg-day for male and 0.72 mg/kg-day for female rats). On the other hand, the discussion in U.S. EPA's Integrated Risk Information System (IRIS, last revised September 1, 1990) uses this same study for calculation of the reference dose (RfD) while identifying a NOAEL of 0.22 mg/kg-day (average of males and females). The supporting IRIS discussion is somewhat confusing, ascribing the 0.22 mg/kg dose to both the 15 ppm level (called a "NOEL" at this point) and the 75 ppm dietary concentration (called a "LEL"). We conclude that 0.22 mg/kg-day is a NOAEL from this study because of the clear dose-response with the three higher doses. However, we acknowledge that lens opacities are not significant by paired t-test at 15 ppm (corresponding to a male/female rat average dose of 0.65 mg/kg).

In a chronic mouse feeding study, 60 CD-1 mice/sex/dose were fed 0, 30, 100, or 300 ppm diquat dibromide for 104 weeks (Hodge, 1991; MRID 42219801). Kidney weight relative to body weight increased slightly but significantly, accompanied by kidney tubule dilation (1/60, 1/60, 3/60, and 6/60 at the four doses), at the two highest doses in males. In female mice, there were increased kidney tubule hyaline droplets at the two highest doses (3/60, 3/60, 10/60, and 11/60 for the respective doses). A significant increase in kidney tubule dilation was also observed at the two highest doses (1/60, 2/60, 4/60, 8/60 for the four doses, respectively) in females. There was a slight increase in lymphoid proliferation in the mesenteric lymph node of the females at 100 ppm (13/59 compared to 9/60 in controls). Eye discharges were also reported to be increased at the two highest doses (DPR, 1994; U.S. EPA, 1995). No evidence of carcinogenicity was observed. The 30 ppm concentration was identified to be the NOAEL, for an effective dose of 3.56 mg/kg-day for male and 4.78 mg/kg-day for female mice, calculated from measured feed consumption. LOAELs were 12 mg/kg-day for male and 16 mg/kg-day for female mice.

In an earlier mouse study, 60 CD-1 mice/sex/dose were fed 0, 30, or 150 ppm diquat dibromide for 80 weeks, with a higher-dose group added during the study (Ben-Dyke et al., 1975). The study had many methodological inadequacies. Reduced growth rates and liver vacuolation were observed, with a NOAEL of 4.5 mg/kg-day and LOAEL of 22.5 mg/kg-day. No carcinogenic effects were observed.

Beagle dogs (four/sex/dose) were fed diquat for one year at doses of 0, 0.5, 2.5, or 12.5 mg/kg-day (Hopkins, 1990; MRID 41730301). Lens opacities were observed in 3/4 male and 3/4 female dogs at the highest dose, and in one (1/4) female dog at 2.5 mg/kg-day. Chronic intestinal inflammatory lesions and kidney weight increases were observed in both sexes at 12.5 mg/kg-day. There was also a decrease in adrenal and epididymal weights in male dogs at 2.5 mg/kg-day. The systemic NOAEL is identified to be 0.5 mg/kg-day, and the LOAEL is 2.5 mg/kg-day.

In another Beagle dog study, three dogs/sex/dose were fed 0, 1.7, 5, or 15 mg/kg-day diquat for two years (Hurst, 1966). One animal of each sex was killed and necropsied at two years, and the study was continued for another two years. Cataracts developed in less than one year at the highest dose, and at 15 to 17 months at the mid-dose level (incidence not specified). No other effects are noted in DPR's (1994) analysis. The "NOEL" for cataracts was identified by DPR to be 1.7 mg/kg-day, with a "LOEL" of 5 mg/kg-day.

Carcinogenicity

Two cancer bioassays have been conducted, one in rats (Colley et al., 1985) and one in mice (Hodge, 1991). These studies are described in detail above, under Chronic Toxicity, because the salient effects were on non-cancer endpoints. There were some apparently random increases in tumors at various doses and sites, but the only result considered to represent potential carcinogenicity was osteosarcomas. The incidence was 0, 1, 0, 0, and 3 osteosarcomas in the male rats at 0, 0.19, 0.58, 2.91, or 14.88 mg/kg-day, respectively. This increase in a rare tumor type was marginally significant by a trend test, but not significant in pairwise comparisons. DPR (1994) and U.S. EPA (1995) concluded that these data were not indicative of carcinogenicity. The bioassay in mice was also concluded to be negative. In female mice there was a significant reduction in the number of tumor-bearing animals.

Based on these data, U.S. EPA rates diquat as Group E, for "evidence of noncarcinogenicity for humans" (U.S. EPA, 1995). However, U.S. EPA's IRIS databank contains no diquat carcinogenicity assessment, and has listed diquat as "under review" for carcinogenicity since at least January 1992.

Toxicological Effects in Humans

Acute Toxicity

Eye, nose, throat, and respiratory irritation may result from acute diquat exposures, possibly accompanied by nausea, vomiting, and diarrhea (Reigart and Roberts, 1999). In herbicidal uses of diquat, exposures to spray aerosols have resulted in severe lung injury, although diquat is less hazardous to pulmonary function than its analogue, paraquat (Wood et al., 1976; Kurisaki and Sato, 1979; Lam et al., 1980; Williams et al., 1986; Reigart and Roberts, 1999). Poisoning by ingestion of these herbicides is more common than by inhalation (Vanholder et al., 1981; Mortensen, 1986; Ameno et al., 1994; Yamashita et al., 1996). The dipyridyl herbicides have been used for many suicides and homicides in Japan, apparently because of the high toxicity and near-certainty of death from ingestion of the consumer products (Yoshioka et al., 1992; Fuke et al., 1996; Yamashita et al., 1996). The estimated human LD_{50} of diquat is 100 mg/kg, although death has occurred from as little as an estimated 67 mg/kg (HSDB, 1998).

Severe skin injuries have resulted in humans from prolonged acute or repeated exposures to the liquid formulation (Manoguerra, 1990; Ronnen et al., 1995). Damage to fingernails (white bands,

possible loss) has also been observed among applicators who repeatedly splash the formulations onto their hands (Samman and Johnston, 1969; Baran, 1974). A single splash of the herbicidal formulations in the eyes can result in severe ocular injury (Cant and Lewis, 1968a,b; Swan, 1968; Nirei et al., 1993).

Accidental ingestion of diquat by a 2 1/2-year old boy resulted in progressive neurologic dysfunction followed by death 143 hours after poisoning. Brain stem lesions were noted post mortem, resembling those noted earlier in some adult diquat poisoning cases (Powell et al., 1983). Neurological, digestive, hepatic, hematological, and renal dysfunction may all be observed (Vanholder et al., 1981; McCarthy and Speth, 1983; Mahieu, 1984; Valiante et al., 1992). There also has been some concern that the dipyridyl herbicides might cause a Parkinson-like syndrome because of the similarity of these compounds to MPTP, a chemical responsible for some cases of drug-induced Parkinsonism (Borm and Van Vliet, 1986; Zilker et al., 1988; Lermontiva et al., 1989; Sechi et al., 1992). The observed neurological effects and brain stem lesions caused by diquat, and a recent report of a paraquat-induced loss of dopaminergic neurons in a mouse model (Brooks et al., 1999) suggest that Parkinson-like effects are indeed possible. Effects on brain dopamine neurons probably require a high dose, although it is possible that diquat may disrupt blood-brain-barrier function under some conditions, thus enhancing diquat uptake into brain.

Gastric lavage and charcoal hemoperfusion can help remove diquat, but may not be successful at alleviating the progressive tissue damage (Hoffman et al., 1983; McCarthy and Speth, 1983). Paraquat appears to be even more difficult to treat after the toxicity ensues (Powell et al., 1983; Wojeck et al., 1983).

Subchronic Toxicity

Repeated dermal exposures to diquat or paraquat have been reported to cause discoloration of fingernails (Samman and Johnston, 1969; Hearn and Keir 1971; Baran, 1974). Other effects may include ocular, oral, nasal, and respiratory irritation. Development of cataracts is a primary concern, based on the animal data, although there are no epidemiological reports of cataracts due to repeated occupational or environmental exposures in humans.

Genetic Toxicity

There are no relevant studies and no evidence of genetic toxicity to humans of diquat or other dipyridyl herbicides.

Developmental and Reproductive Toxicity

No information is available on developmental or reproductive toxicity of diquat in humans.

Immunotoxicity

No reports were found on immunotoxic effects of diquat in humans.

Neurotoxicity

Severe neurotoxic effects of diquat are observed after high doses of diquat (Powell et al., 1983; McCarthy and Speth, 1983), in contrast to paraquat (Reigart and Roberts, 1999). Neuropathy

should be considered in evaluating the effects of occupational exposures. There has been one report of Parkinson-like symptoms after acute diquat exposures (Sechi et al., 1992). The potential for uptake of diquat and other charged pyridyl compounds into dopamine neurons, which might produce oxidative damage (Schapira, 1995) and result in Parkinsonian symptoms, remains under investigation (Brooks et al., 1999). Several epidemiologic studies have suggested a possible association of Parkinsonism with herbicides or pesticides (Semchuck et al., 1992; Hubbel et al., 1993; Liou et al., 1997; Gorell et al., 1998; Checkoway and Nelson, 1999). However, there is inadequate evidence at this time to support the hypothesis of a causative relationship between exposure to the dipyridyls and Parkinsonism or any other neurotoxic effects in humans.

Chronic Toxicity

No reports of toxic human effects associated with chronic exposures to diquat were found.

Carcinogenicity

There is no information to suggest a relationship between diquat and human cancers. Studies in animals were considered by both DPR and U.S. EPA to be negative for carcinogenicity.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The critical effects for calculation of a PHG are lens opacities and cataracts in rats (Colley et al., 1985) and dogs (Hopkins, 1990) in dietary exposure studies, and developmental abnormalities observed in a rabbit gavage exposure (Hodge, 1989). Maternal and developmental effects in mice after gavage exposures represent a supporting sensitive endpoint (Palmer et al., 1978). There were no available chronic studies of diquat supplied in the drinking water.

In the chronic rat study of Colley et al. (1985), incidence of lens opacities in response to dietary diquat was very low at the lower doses, but showed a good dose-response relationship. The LOAEL after two-years exposure was estimated to be 15 ppm for lenticular opacities in both male and female rats, with a NOAEL of 5 ppm. This represents doses (average of male and female rats) of 0.65 mg/kg-day and 0.22 mg/kg-day for the LOAEL and NOAEL, respectively. We conclude that these values are an appropriate basis for risk assessment of exposure to diquat in drinking water.

The Hopkins (1990) report of cataracts and other adverse effects in dogs after one-year exposures to diquat in food should also be considered in developing a PHG for diquat. In this study, the LOAEL for lens opacities and decreased adrenal and epididymal weights in male dogs was 2.5 mg/kg-day, with an experimental NOAEL of 0.5 mg/kg-day.

The developmental effects in rabbits (Hodge, 1989) were delayed ossification and various malformations possibly associated with a common mechanism, interference with cell migration (DPR, 1994). In these effects, the number of affected fetuses was small, without a clear dose-response between 1 mg/kg and 10 mg/kg (see Table 2). The appropriate uncertainty factor to use for estimation of a NOAEL from these data is somewhat equivocal, considering that the fetal LOAEL has been identified to be 1 mg/kg-day by one set of reviewers (DPR, 1994) and 10 mg/kg-day by another (U.S. EPA, 1995). In the same study, the maternal NOAEL was identified to be 3 mg/kg-day by DPR (1994) and 1 mg/kg-day by U.S. EPA (1995). DPR has

chosen an uncertainty factor of three from the fetal LOAEL of 1 mg/kg, "[b]ecause the magnitude (incidence) of the effect was small, and the slope of the dose-response was fairly shallow." This use of an uncertainty factor of three and the rationale are consistent with earlier risk assessment recommendations (Dourson and Stara, 1985; U.S. EPA, 1987). This results in an estimated NOAEL of 0.33 mg/kg-day. The gavage mode of administration used in this study would be expected to result in higher peak blood levels and toxic effects than in exposures to diquat in drinking water or diet.

A fourth study that resulted in low-dose toxicity estimates was the Palmer et al. (1978) developmental study of diquat administered by gavage to mice. In this study, adverse maternal and fetal effects were observed at 2 and 4 mg/kg-day. The observed NOEL was 1 mg/kg-day for both dams and fetuses. Again, gavage administration should result in higher peak levels of diquat than would be expected from diquat in drinking water.

Taken together, these four studies indicate that the chronic NOAEL should be considered to be less than 1 mg/kg-day. The diquat PHG will be calculated based on the rat NOAEL of 0.22 mg/kg-day for eye opacities (Colley et al., 1985), which is slightly lower than the corresponding dog NOAEL of 0.5 mg/kg-day for eye opacities. According to our guidelines, where the studies are of comparable quality, results from the more sensitive species should be chosen. The use of a NOAEL of 0.22 mg/kg-day for risk assessment should also protect against developmental effects, for which there was an estimated and comparable NOAEL of 0.33 mg/kg-day in rabbits (DPR, 1994, based on Hodge, 1989).

For the calculation of the PHG, the standard uncertainty factors of 10 for interspecies extrapolation and 10 for potential sensitive subpopulations should be adequate to protect humans against adverse effects. This risk analysis explicitly considers the potential for developmental effects. Therefore, no additional safety or uncertainty factor appears to be needed to ensure protection of infants and children.

Because the diquat toxicity estimate is to be used for exposure to diquat in drinking water, no additional consideration of the low absorbed dose by the gastric route is necessary. However, to the extent that additional exposure by other routes is possible, combined exposure estimates should consider route-specific absorption fractions. We recommend 10 percent for oral exposure to diquat in food or water, 1 percent for dermal exposure to diquat in water, 0 percent for oral or dermal exposure to diquat bound to soil, and 70 percent for inhalation exposure to respirable-size particles in aqueous aerosols of diquat.

CALCULATION OF PHG

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for the herbicide diquat in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times W}$$

where,

NOAEL/LOAEL	=	no-observed-adverse-effect-level or lowest-observed-adverse-effect-level,
BW	=	body weight (a default of 70 kg for an adult male, 60 kg for an adult female, or 10 kg for a child),
RSC	=	relative source contribution (defaults of 0.2, 0.4, and 0.8 to account for 20, 40, or 80 percent of the total exposure expected or allowed to be derived from drinking water),
UF	=	uncertainty factors (typical defaults of 10 to account for inter-species extrapolation and 10 for potentially sensitive human subpopulations; other factors may be incorporated for extrapolation from a subchronic study or to account for severity of effect), and
W	=	daily water consumption rate (typically 2 L/day for a 60 to 70 kg adult and 1 L/day for a 10 kg child, where applicable).

In this case, the RSC is set at 0.2 to allow for exposure to diquat residues in food. There is also a possibility of some exposure to diquat in aerosol droplets during showering. Consideration of aerosol exposures acknowledges that diquat is much more toxic by inhalation than by oral administration because of more efficient absorption after inhalation, although the fraction of the total diquat in respirable-size particles would be extremely small. Body weight is assumed to be 70 kg and water consumption 2 L/day as the standard defaults for lifetime exposures of the whole population. The uncertainty factor is set at 100 to include ten for intraspecies extrapolation and ten for potential sensitive populations.

Therefore,

$$C = \frac{0.22 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{100 \times 2 \text{ L/day}} = 0.015 \text{ mg/L} = 15 \text{ ppb}$$

Based on this calculation and the NOAEL of 0.22 mg/kg-day for minimal lens opacities and cataracts in chronic dietary exposures of rats to diquat dibromide, a PHG of 0.015 mg/L (15 ppb) is calculated for diquat in drinking water. Reported cataracts in dogs and developmental effects in rabbits and mice at slightly higher exposure levels support the selection of the NOAEL for ocular effects in rats.

RISK CHARACTERIZATION

There are significant differences of scientific opinion among reviewers in interpretation of the critical animal studies. We have accepted the more health-protective interpretations of the rat data on lens opacities to estimate a NOAEL of 0.22 mg/kg-day from the data on cataracts in rats after two-year dietary exposures (Colley et al., 1985) on which to base the PHG. Our evaluation of the reports on developmental effects of diquat concluded that this effect has been adequately characterized by both DPR and U.S. EPA as having a greater NOAEL than that estimated above for the lens opacities. In addition, the gavage administration in the developmental study is likely to cause greater peak levels and greater acute toxic effects than administration of diquat in the diet or in drinking water. The dietary studies are therefore judged to be more relevant for calculation of the PHG.

Inhalation exposures are considerably more toxic than are oral or dermal exposures. This is largely because of greater bioavailability for diquat by inhalation, rather than a selective lung effect as for paraquat. The subchronic inhalation LOAEL for diquat is estimated to be 0.02 mg/kg-day, based on two rat studies involving daily exposures to diquat aerosol droplets (Bruce and Griffis, 1987; U.S. EPA, 1995). Some exposure to aerosolized diquat may occur in showering, but there are no data to justify a quantitative exposure assessment. The low volatility and high water solubility of diquat should result in no significant exposure to diquat in the vapor phase. Dermal uptake of diquat should be comparatively insignificant from all sources.

The uncertainties in this risk assessment are reflected by the use of a combined uncertainty factor (UF) of 100, which represents extrapolation to a safe dose in humans from animal data, and uncertainty concerning possible sensitive human subpopulations. There is also considerable uncertainty about the RSC, which has been set to a default value of 0.2 for a pesticide with significant food uses. Inadequate data were available on distributions in food and drinking water to calculate an RSC for this chemical.

Little or no information exists on potential long-term effects of diquat in humans. However, because diquat is not routinely found in drinking water in California (DPR, 1999), this does not represent a critical data limitation. OEHHA believes that the PHG of 0.015 mg/L (15 ppb) is adequate and appropriate to protect humans, including infants, children, and other potential sensitive populations against adverse effects of diquat in drinking water.

OTHER REGULATORY STANDARDS

U.S. EPA's maximum contaminant level (MCL) and maximum contaminant level goal (MCLG) for diquat are both 0.02 mg/L (20 ppb) (U.S. EPA, 1990; IRIS, 1999). The California MCL is also 0.02 mg/L (CCR Title 22, Sec. 64444(b)). According to IRIS, U.S. EPA's RfD for diquat is 0.0022 mg/kg-day, based on "minimal lens opacity and cataracts" in a study identified as "Chevron Chemical, 1985." This is the rat dietary study identified in this document as Colley et al. (1985).

REFERENCES

Adam A, Smith LL, Cohen GM (1990) a. An evaluation of the redox cycling potencies of paraquat and nitrofurantoin in microsomal and lung slice systems. Biochem Pharmacol 40(7):1533-9.

Adam A, Smith LL, Cohen GM (1990) b. An assessment of the role of redox cycling in mediating the toxicity of paraquat and nitrofurantoin. Environ Health Perspect 85:113-7.

Ahmed FE, Hart RW, Lewis NJ (1977). Pesticide induced DNA damage and its repair in cultured human cells. Mut Res 42:161-74.

Ameno K, Fuke C, Shirakawa Y, Ogura S, Ameno S, Kiriu T, Kinoshita H, Ijiri I (1994). Different distribution of paraquat and diquat in human poisoning cases after ingestion of a combined herbicide. Arch Toxicol 68(2):134-7.

Anton P, Theodorou V, Fioramonti J, Bueno L (1998). Low-level exposure to diquat induces a neurally mediated intestinal hypersecretion in rats: involvement of nitric oxide and mast cells. Toxicol Appl Pharmacol 152(1):77-82.

Auletta CS (1987). A twenty-one day dermal toxicity study in rats with diquat technical Chevron Study No. S-2907. DPR Vol. 226-065 #062368.

Awad JA, Burk RF, Roberts LJ (1994). Effect of selenium deficiency and glutathione-modulating agents on diquat toxicity and lipid peroxidation in rats. J Pharmacol Exp Ther 270(3):858-64.

Baran RL (1974). Nail damage caused by weed killers and insecticides. Arch Dermatol 110(3):467.

Ben-Dyke R, Strachan E, Newman AJ (1975). Diquat dibromide monohydrate: evaluation of potential carcinogenicity in dietary administration to mice for 80 weeks. LSR Report No. 76/ILY1/144. DPR Vol. 226-032 #037767.

Benigni R, Bignami M, Carere A, Conti G, Conti L, Crebelli R, Dogliotti E, Gualandi G, Novelletto A, Ortali VA (1979). Mutational studies with diquat and paraquat in vitro. Mut Res 68:183-9.

Bignami M, Crebelli R (1979). A simplified method for the induction of 8-azaquanine resistance in Salmonella typhimurium. Toxicol Lett 3:169-75.

Blakeman DP, Ryan TP, Jolly RA, Petry TW (1998). Protein oxidation: examination of potential lipid-independent mechanisms for protein carbonyl formation. J Biochem Mol Toxicol 12(3):185-90.

Borm PJ, Van Vliet C (1988). Susceptibility in Parkinson's disease. "Of mice and men." Med Hypotheses 27(3):205-7.

Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ (1999). Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res 823:1-10.

Bruce ED (1985). The acute inhalation toxicity of diquat water weed killer (SX-1574) in rats. DPR Vol. 226-041, #048868 (also U.S. EPA Access #26385, as cited in U.S. EPA, 1995).

Bruce ED, Griffis LC (1987). Three-week satellite aerosol inhalation toxicity study of diquat concentrate (SX-1750) in rats. SOCAL #2353, DPR Vol. 226-078, #071176.

Cant JS, Lewis DR (1968) a. Ocular damage due to paraquat and diquat. Br Med J 2(599):224.

Cant JS, Lewis DR (1968) b. Ocular damage due to paraquat and diquat. Br Med J 3(609):59.

Charles JM, Abou-Donia MB, Menzel DB (1978). Absorption of paraquat and diquat from the airways of the perfused rat lung. Toxicology 9:59-67.

Checkoway H, Nelson LM (1999). Epidemiologic approaches to the study of Parkinson's disease etiology. Epidemiology 10(3):327-36.

Clark DG, Hurst EW (1970). The toxicity of diquat. Brit J Ind Med 27:51-5.

Colley J, Edmonson J, Heywood R, Street AE, Prentice DE, Gallagher PJ, Gibson WA, Cherry CP (1981). Diquat dibromide: preliminary assessment of toxicity to rats by dietary administration for 4 weeks, final report. ICI Study No. 383/80935. DPR Vol. 226-051 #058114.

Colley J, Warren S, Heywood R, Street AE, Almond RH, Gopinath C (1985). Diquat dibromide: evaluation of potential carcinogenicity and chronic toxicity by prolonged dietary administration to rats. ICI Study No. CTL/C/1327A. DPR Vol. 226-025 #037760. Cited by IRIS as Chevron Chemical Company, 1985; MRID 00145855, 00155474, and 00160673.

Czyzewska K, Knapowski J, Kontek M (1984). Paraquat effect on the bioelectric parameters of the rabbit small intestine and its in vitro penetration. Acta Physiol Pol 35(1):107-13.

Czyzewska K, Junik R, Knapowski J (1985). Changes of transport functions of rabbit small intestinal wall under the effect of diquat and its penetration in vitro. Acta Med Pol 26:13-25.

Daniel JW, Gage JC (1966). Absorption and excretion of diquat and paraquat in rats. Brit J Industr Med 23:131-6.

DeGray JA, Rao DN, Mason RP (1991). Reduction of paraquat and related bipyridylium compounds to free radical metabolites by rat hepatocytes. Arch Biochem Biophys 289(1):145-52.

Dourson ML, Stara JF (1985). The conceptual basis of the acceptable daily intake. U.S. EPA Environmental Criteria and Assessment Office, Cincinnati, Ohio.

DPR (1994). Diquat dibromide, risk characterization document. Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California.

DPR (1996). Pesticide Use Report, Annual 1995. Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California.

DPR (1999) a. Summary of Pesticide Use Report Data, 1997. Department of Pesticide Regulation, Cal/EPA, Sacramento, California.

DPR (1999) b. Well Inventory Reports for 1996 and 1997, available online at http://www.cdpr.ca.gov. Department of Pesticide Regulation, Cal/EPA, Sacramento, California.

FAO. (1971). 1970 Evaluations of Some Pesticide Residues in Food. United Nations Food and Agriculture Organization. Rome, Italy. DPR Vol. 226-002 #916123. (as cited in DPR, 1994)

Feldmann RJ, Maibach HI (1974). Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 29:126-32.

Fletcher K, Griffiths D, Kinch DA (1972). Diquat dibromide: three-generation reproduction study in rats. ICI Study No. HO/IH/R/334A. DPR Vol. 226-005 #916116.

Fuke C, Ameno K, Ameno S, Kinoshita H, Ijiri I (1996). Detection of two metabolites of diquat in urine and serum of poisoned patients after ingestion of a combined herbicide of paraquat and diquat. Arch Toxicol 70(8):504-7.

Fuke C, Ameno K, Ameno S, KiriuT, Shinohara T, Ijiri I (1993). In vitro studies of the metabolism of paraquat and diquat using rat liver homogenates -- isolation and identification of the metabolites of paraquat and diquat. Nippon Hoigaku Zasshi 47(1):33-45.

Gaines TB, Linder RE (1986). Acute toxicity of pesticides in adult and weanling rats. Fundam Appl Toxicol. 7(2):299-308.

Gallagher EP, Buetler TM, Stapleton PL, Wang C, Stahl DL, Eaton DL (1995). The effects of diquat and ciprofibrate on mRNA expression and catalytic activities of hepatic xenobiotic metabolizing and antioxidant enzymes in rat liver. Toxicol Appl Pharmacol 134(1):81-91.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ (1998). The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50(5):1346-50.

Griggs RE, Davis JA (1973). Diquat: excretion and metabolism in a goat. ICI Study No. AR 2585A. DPR Vol. 226-018 #011320.

Hearn CE, Keir W (1971). Nail damage in spray operators exposed to paraquat. Br J Ind Med 28(4):399-403.

Hemingway RJ, Leahey JP, Davis JA, Burgess JG (1974). Metabolism of diquat and its photoproducts in a cow. ICI Study No. AR 2530B. DPR Vol. 226-018 #011322.

Hodge MCE (1989). Diquat: teratogenicity study in the rabbit. ICI Study No. CTL/P/2379. DPR Vol. 226-088 #075530.

Hodge MCE (1990). Diquat: multigeneration study in the rat. ICI Study No. RR0393. DPR Vol 226-090 #091173.

Hodge MCE (1991). Diquat: two year feeding study in mice. ICI Study No. PM0749. DPR Vol. 226-098 #112959.

Hoffman S, Jedeikin R, Korzets Z, Shapiro AL, Kaplan R, Bernheim J (1983). Successful management of severe paraquat poisoning. Chest 84(10):107-9.

Hopkins MN (1990). Diquat: one year feeding study in dogs. ICI Study No. CTL/P/2596. DPR Vol. 226-094 #089037.

Horner JM (1992) a. Diquat: acute neurotoxicity study in rats. ICI Report No. CTL/P/3789. DPR Vol. 226-102 #120645.

Horner JM (1992) b. Diquat: subchronic neurotoxicity study in rats. ICI Report No. CTL/P/3751. DPR Vol. 226-101 #120427.

HSDB (1998). Diquat. Hazardous Substances Data Bank, accessed online at http://toxnet.nlm.nih.gov.

Hubbel JP, Cao T, Hassanein RE, Neuberger JS, Koller WC. 1993. Risk factors for Parkinson's disease. Neurology 43(9):1693-7.

Hurst EW (1966). A long-term toxicity test with diquat dichloride monohydrate in dogs. ICI Study No. IHR/195. DPR Vol. 226-031 #037766.

IRIS (1999). Diquat (RfD last revised September 1, 1990). U.S. EPA Integrated Risk Information System, available online at http://www.epa.gov/ngispgm3/iris.

Kurisaki E, Sato H (1979). Tissue distribution of paraquat and diquat after oral administration in rats. Forensic Sci Int 14(3):165-70.

Lam HF, Takezawa J, Gupta BN, van Stee EW (1980). A comparison of the effects of paraquat and diquat on lung compliance, lung volumes and single breath diffusing capacity in the rat. Toxicology 18(20):111-23.

Langston JW (1998). Epidemiology versus genetics in Parkinson's disease: progress in resolving an age-old debate. Ann Neurol 44(3 Suppl 1):S45-52.

Lermontiva NN, Soliakov LS, Bachurin SO, Tkachenko SE, Serkova TP (1989). Evaluation of the capability of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and pyridine derivatives to evoke Parkinsonism. Biull Eksp Biol Med 107(6):699-701.

Lindquist NG, Larsson BS, Lyden-Sokolowski A (1988). Autoradiography of [^{14}C]paraquat or [^{14}C]diquat in frogs and mice: accumulation in neuromelanin. Neurosci Lett 93(1):1-6.

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC (1997). Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 48(6):1583-8.

Litchfield HH, Danier JW, Longshaw S (1973). The tissue distribution of the bipyridylium herbicides diquat and paraquat in rats and mice. Toxicology 1:155-65.

Mahieu P, Bonduelle Y, Bernard A, De Cabooter A, Gala M, Hassoun A, Koenig J, Lauwerys R (1984). Acute diquat intoxication. Interest of its repeated determination in urine and the evaluation of renal proximal tubule integrity. J Toxicol Clin Toxicol 22(4):363-9.

Manoguerra AS (1990). Full thickness skin burns secondary to an unusual exposure to diquat dibromide. J Toxicol Clin Toxicol 28(1):107-10.

McCarthy LG, Speth CP (1983). Diquat intoxication. Ann Emerg Med 12(60):394-6.

McGregor DB (1974). Dominant lethal study in mice of diquat. Inveresk Research Int. Study No. 401567. DPR Vol. 226-001 #916118.

Merck Index (1996). Diquat dibromide. The Merck Index, 12th Ed. Merck & Co., Inc., Whitehouse Station, NJ, p. 568.

Mills IH (1976). Diquat: Disposition and metabolism in the rat. ICI Study No. CTL/P/214. DPR Vol. 226-018 #043645.

Minakata K, Suzuki O, Oh-ishi S, Hayashi I, Saito S, Harada N (1995). Diquat increases cysteine proteinase inhibitors greatly in rat plasma and tissues. Arch Toxicol 69(5):318-21.

Montgomery JH (1993). Agrochemicals Desk Reference, Environmental Data. Lewis Publishers, Boca Raton, FL, pp. 180-1.

Mortensen ML (1986). Management of acute childhood poisonings caused by selected insecticides and herbicides. Pediatr Clin North Am 33(2):421-45.

Nirei M, Hayasaka S, Nagata M, Tamai A, Tawara T (1993). Ocular injury caused by Preeglox-L, a herbicide containing paraquat, diquat, and surfactants. Jpn J Opthalmol 37(1):43-6.

Palmer AK, Edwards JA, Woodhouse RN (1977). Preliminary toxicity studies to determine the effect of diquat on the mouse. ICI Study No. CTL/O/330. DPR Vol. 226-074 #066521.

Palmer AK, Edwards JA, Woodhouse RN (1978). Effect of diquat on pregnancy of the mouse. ICI Study No. ICI/167/77642. DPR Vol. 226-001 #916114.

Palmer S, Pratt IS (1974). Diquat dibromide: teratogenic studies in the rabbit. ICI Study No. HO/CTL/P/114B. DPR Vol. 226-001 #916113.

Powell D, Pond SM, Allen TB, Portale AA (1983). Hemoperfusion in a child who ingested diquat and died from pontine infarction and hemorrhage. J Toxicol Clin Toxicol 20(5):405-20.

Rajput AH, Uitti RJ, Stern W, Laverty W, O'Donnell K, O'Donnell D, Yuen WK, Dua A. Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. Can J Neurol Sci 14(3 Suppl):414-8.

Rawlings JM, Foster JR, Heylings JR (1992). Diquat-induced intestinal secretion in the anaesthetized rat. Hum Exp Toxicol 11(6):524-9.

Rawlings JM, Wyatt I, Heylings JR (1994). Evidence for redox cycling of diquat in rat small intestine. Biochem Pharmacol 47(7):1271-4.

Reigart JR, Roberts JR (1999). Paraquat and diquat. In: Recognition and Management of Pesticide Poisonings, 5th Ed. U.S. Environmental Protection Agency, EPA-735-R-98-003, pp. 108-17.

Richardson CR, Howard CA, Wildgoose J (1986). Diquat dibromide (technical): a cytogenetics study in human lymphocytes in vitro. ICI Study No. CTL/P/1561. DPR Vol. 226-049 #057734.

Rikans LE, Cai Y (1993). Diquat-induced oxidative damage in BCNU-pretreated hepatocytes of mature and old rats. Toxicol Appl Pharmacol 118(2):263-70.

Rikans LE, Cai Y, Kosanke SD, Venkataraman PS (1993). Redox cycling and hepatotoxicity of diquat in aging male Fischer 344 rats. Drug Metab Dispos 21(4):605-10.

Ronnen M, Klin B, Suster S (1995). Mixed diquat/paraquat-induced burns. Int J Dermatol 34(1):23-5.

Saito K (1986). Effect of cations and some compounds on paraquat accumulation into cultured pneumocytes. Tohoku J Exp Med 148(1):41-7.

Samman PD, Johnston EN (1969). Nail damage associated with handling of paraquat and diquat. Br Med J 1(647):818-9.

Sandy, MS, Moldeus P, Ross D, Smith MT (1987). Cytotoxicity of the redox cycling compound diquat in isolated hepatocytes: involvement of hydrogen peroxide and transition metals. Arch Biochem Biophys 259(1):29-37.

Schapira AH (1995). Oxidative stress in Parkinson's disease. Neuropathol Appl Neurobiol 21(1):3-9.

Sechi GP, Agnetti V, Piredda M, Canu M, Deserra F, Omar HA, Rosati G (1992). Acute and persistent Parkinsonism after use of diquat. Neurology 42(1):261-3.

Semchuk KM, Love EJ, Lee RG (1992). Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 42(7):1328-35.

Shaw B, Hopke PK (1975). The dynamics of diquat in a model eco-system. Environ Lett 8(4):325-35.

Sheldon T, Richardson CR, Shaw J (1986). Diquat dibromide (technical): an evaluation in the mouse micronucleus test. ICI Study No. CTL/P/1532. DPR Vol. 226-049 #057732.

Smith CV (1987). Evidence for participation of lipid peroxidation and iron in diquat-induced hepatic necrosis in vivo. Mol Pharmacol 32(3):417-22.

Smith CV, Hughes H, Lauterburg BH, Mitchell JR (1985). Oxidant stress and hepatic necrosis in rats treated with diquat. J Pharmacol Exp Ther 235(1):172-7.

Spalding DJ, Mitchell JR, Jaeschke H, Smith CV (1989). Diquat hepatotoxicity in the Fischer-344 rat: the role of covalent binding to tissue proteins and lipids. Toxicol Appl Pharmacol 101(2):319-27.

Stevens MA, Walley JK (1966). Tissue and milk residues arising from the ingestion of single doses of diquat and paraquat by cattle. J Sci Fd Agric 17:472-5 (as cited in DPR, 1994).

Swan AA (1968). Ocular damage due to paraquat and diquat. Br Med J 2(605):624.

Swan AAB (1963). The dermal toxicity of diquat dichloride. ICI Study No. TR/540. DPR Vol. 226-005 #916104.

Tanner CM (1989). The role of environmental toxins in the etiology of Parkinson's disease. Trends Neurosci 12(2):49-54.

Tanner CM, Chen B, Wang WZ, Peng ML, Liu ZL, Liang XL, Kao LC, Gilley DW, Schoenberg BS (1987). Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci 14(3):419-23.

Trueman RW (1986). Diquat dibromide (technical): assessment for the induction of unscheduled DNA synthesis in rat hepatocytes in vivo. ICI Study No. CTL/P/1814. DPR Vol. 226-062 #062163.

Tsokos-Kuhn JO, Smith CV, Hughes H, Mitchell JR (1988). Liver membrane calcium transport in diquat-induced oxidative stress in vivo. Mol Pharmacol 34(2):209-14.

U.S. EPA (1987). Reference Dose (RfD): Description and Use in Health Risk Assessments. Integrated Risk Information System, Appendix A. Intra-Agency Reference Dose Work Group, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

U.S. EPA (1990). Organic chemical standards, 55 FR 30370, 07/25/90.

U.S. EPA (1995). R.E.D. facts, diquat dibromide. Office of Prevention, Pesticides, and Toxic Substances, July 1995. EPA 738-F-95-015.

Valiante F, Farinati F, Dal Santo P, Germana B, Di Marlo F, Naccarato R (1992). Upper gastrointestinal injury caused by diquat. Gastrointest Endosc 38(2):204.

Vanholder R, Colardyn F, De Reuck J, Praet M, Lameire N, Ringoir S (1981). Diquat intoxication: report of two cases and review of the literature. Am J Med 70(6):1267-71.

Vulimiri SV, Gupta S, Smith CV, Moorthy B, Randerath K (1995). Rapid decreases in indigenous covalent DNA modifications (I-compounds) of male Fischer-344 rat liver DNA by diquat treatment. Chem Biol Interact 95:1-16.

Wester RC, Maibach HI (1985). In vivo percutaneous absorption and decontamination of pesticides in humans. J Toxicol Environ Health 16:25-37.

Wickramaratne GA (1989). Diquat: teratogenicity study in the rat. ICI Study No. CTL/P/2331. DPR Vol. 226-089 #075531.

Wildgoose J, Braithwaite I, Howard CA, Richardson CR (1986). Diquat dibromide: a cytogenetic study in human lymphocytes in vitro. ICI Study No. CTL/P/1469. DPR Vol. 226-049 #057733.

Williams PF, Jarvie DR, Whitehead AP (1986). Diquat intoxication: treatment by charcoal haemoperfusion and description of a new method of diquat measurement in plasma. J Toxicol Clin Toxicol 24(10):11-20.

Wojeck GA, Price JF, Nigg HN, Stamper JH (1983). Worker exposure to paraquat and diquat. Arch Environ Contam Toxicol 12(1):65-70.

Wood TE, Edgar H, Salcedo J (1976). Recovery from inhalation of diquat aerosol. Chest 70:774-5.

Yamashita M, Matsuo H, Tanaka J, Yamashita M (1996). Analysis of 1,000 consecutive cases of acute poisoning in the suburb of Tokyo leading to hospitalization. Vet Hum Toxicol 38:34-5.

Yoshioka T, Sugimoto T, Kinoshita N, Shimazu T, Hiraide A, Kuwagata Y (1992). Effect of concentration reduction and partial replacement of paraquat by diquat on human toxicity: a clinical survey. Hum Exp Toxicol 11:241-5.

Zilker T, Fogt F, von Clarmann M (1988). No Parkinsonian syndrome following acute paraquat poisoning. Klin Wochenschr 66(22):1138-41.